Malignant neoplasms following cardiac transplantation

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Abstract

Objective: Malignancies have long been recognized as a complication of long lasting immunosuppressive therapy. We reviewed our experience to investigate the incidence and the spectrum of non cutaneous de novo malignant neoplasms. Methods: Between March 1987 and March 1996, 296 patients underwent 303 cardiac transplantation in our service. The population at risk consists of all patients surviving more than 1 month after transplantation, leading to a total of 267 patients. A triple-immunosuppressive therapy was employed. Moderate doses of antilymphocyte globulin was used as an induction immunotherapy. Results: Neoplasms developed in 18 (6.7%) of the 267 patients at risk. Seventeen patients were male. Mean age was 56 ± 7 years. Fourteen patients (78%) reported a significant smoking history. Mean interval between transplantation and clinical diagnosis was 36 months. Lung neoplasms (especially adenocarcinoma) were the most commonly encountered tumors (11 of 268 patients, 4.1%). Three Non-Hodgkins' Lymphoma (NHL) were identified (1.1%). No Kaposi's sarcoma were diagnosed. Mean survival after a diagnostic of tumor was 11.7 months. Conclusions: The incidence of NHL is low in our transplant recipients. Conversely, we observed a high incidence of lung neoplasms (especially adenocarcinoma) which can be correlated with a heavy cigarette use in the study population. © 1997 Elsevier Science B.V.

Keywords: Heart transplantation; Malignancies; Immunosuppression

1. Introduction

De novo malignant neoplasms, especially lymphoproliferative disorders, have long been recognized as a complication of organ transplantation [10]. Severe immunosuppression associated with organ transplantation clearly predisposes patients to an increased risk of malignancies [11]. We reviewed our 9-year cardiac transplantation experience to investigate the incidence and the spectrum of non cutaneous de novo malignant neoplasms.

2. Patients and methods

Between March 1987 and March 1996, 296 patients underwent 303 orthotopic cardiac transplant procedures in our service. The population at risk consists of all patients surviving more than 1 month after transplantation, leading to a total of 267 patients. Those 267 patients were prospectively follow-up in the cardiac transplantation program at Hopital Louis Pradel. None of them was lost to follow-up.
A standard immunosuppressive program was used to treat these patients according to the following regimen:
1. Administration of cyclosporine (4 mg/kg per day) was started on the second post operative day in two divided doses and was adjusted according to serum creatinine levels and monitoring of serum cyclosporine levels (radioimmunoassay). Cyclosporine therapy was adjusted during the first month to a target level between 200 and 300 ng/mL, 100 to 200 ng/mL between months 1 and 6, and around 100 ng/mL thereafter.
2. Recipients received methylprednisolone (500 mg) intravenously at the end of cardiopulmonary bypass. Steroids were maintained intravenously at an initial dosage of 1 mg/kg per day, then given orally on the fourth postoperative day, and ultimately tapered so that all patients received 0.2 mg/kg per day at 2 months.
3. Azathioprine was started on the second post operative day at 2 mg/kg per day. The dose was adjusted to maintain a white blood count of at least 4000/mm³. Azathioprine was stopped in case of bone marrow or hepatic toxic reactions.
4. Rabbit antilymphocyte serum (polyclonal antilymphocyte immunoglobulin) was begun 24 h after transplantation and administered intravenously at a dosage of 100 mg/day every other day for the first week.
5. Anti-CD3 immunoglobulin 'induction' (OKT3) therapy was used in case of renal insufficiency. That therapy was begun immediately after transplantation and given intravenously daily for 10 days at the dose of 5 mg. Cyclosporine was introduced on day 10.

Acute rejection episodes were treated with intravenous daily doses of methylprednisolone (1 g) for 3 days. If rejection persisted after 1 week or in case of severe rejection episodes, rabbit antilymphocyte sera were added (100 mg intravenous daily dose for 3 days). OKT3 therapy was administrated for 10 days in case of severe recurrent rejection episodes or rejection episodes associated with renal insufficiency in hemodynamically unstable patients.

After discharge from the hospital, clinical follow-up was carried out every month for 6 months, every 2 months for the remainder first year, and annually thereafter. Patients underwent echocardiography and endomyocardial biopsy according to our department criteria [6]. Patients were routinely monitored for evidence of Epstein-Barr virus (EBV) infection. The diagnosis of active EBV infection was defined as a positive immunoglobulin M titer or a rise of fourfold or greater in immunoglobulin G titer (Immunofluorescence of the capsid antibody). Screening for neoplasia was an integral part of the follow-up. That screening was carried out by history, physical exam, chest radiography, and if indicated, specific investigations (scanner, serum markers...).

Records and pathology reports of patients in whom malignant neoplasms occurred (study population) were retrospectively reviewed in detail. Chi-square and t-tests were used to compare differences between groups analysed (study population; transplant population at risk) for statistical significance. The actuarial probability of survival was calculated from the date of cardiac transplantation according to the method of Kaplan and Meier. Statistical significance between actuarial curves was determined according to the Log-Rank Test (Statistica software).

3. Results

3.1. Patients characteristics

Non cutaneous malignant neoplasms developed in 18 (6.7%) of the 267 patients at risk. Seventeen patients (94%) were male, a sex difference significantly (P = 0.001) greater than that of the population at risk (patients surviving more than 1 month). Mean age at the time of transplantation was 56 ± 7 years (range, 42 to 66 years) significantly older than the transplant population at large (P = 0.002). Eight patients (45%) underwent transplantation for idiopathic cardiomyopathy, 6 (33%) for ischemic cardiomyopathy and 4 (22%) for other diagnoses. Among the nineteen patients, 9 (50%) were type O blood, 4 (22%) were type A blood, 3 were type B blood and 1 was type AB blood. A comparison between the study population and the transplant recipients at large is summarized in Table 1. Fourteen patients (78%) reported a significant smoking history averaging 40 pack-years (range 15 to 70 pack-years). The frequency of acute rejection episodes was 1.6 for the first 12 months after heart transplantation. Mean cyclosporine daily dose, available for 17 patients of the study population, was 4.9 mg/kg 1 year after transplan-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics of study population and transplant population at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Study population</td>
</tr>
<tr>
<td>No. of patients</td>
<td>18</td>
</tr>
<tr>
<td>Age (years) Mean ± standard deviation</td>
<td>56 ± 7</td>
</tr>
<tr>
<td>Male (%)</td>
<td>94</td>
</tr>
<tr>
<td>Cardiomyopathy (%)</td>
<td>45</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>33</td>
</tr>
<tr>
<td>Ischemic</td>
<td>22</td>
</tr>
</tbody>
</table>

*P = 0.002; bP = 0.001; cNon significant.
Fig. 1. Comparative actuarial survival in the two groups of patients.

Augmented immunotherapy for rejection: 8 (44%) of the 18 patients received augmented immunotherapy for rejection: 6 patients were treated with polyclonal antilymphocyte immunoglobulin; 2 patients received polyclonal associated with monoclonal immunoglobulins (OKT3) for 10 days. No patients had an active EBV infection.

3.2. Malignancies: diagnosis and specificity

The mean interval between transplantation and clinical diagnosis of malignancy was 36 months with a range of 6 to 96 months. The eighteen non cutaneous de novo malignancies were separated into two groups: Non-Hodgkins' Lymphoma (NHL) and Non Cutaneous Solid Malignancies (NCSM). There were 3 cases of NHL (1.1%) and 15 cases of NCSM (5.6%). No Kaposi's sarcoma were diagnosed in the population at risk.

In the group of NHL, mean interval between transplantation and clinical diagnosis was 55 months. The three of them were aggressive NHL. The histologic grades were not available except one Burkitt lymphoma. The site of involvement were disseminated in one case, localised with lymphadenopathy in two cases (one case of mediastinal and one case of retroperitoneal lymphadenopathy). All of the 3 patients needed augmented immunotherapy for acute rejection episodes during the first year. One of them presented severe and multiple acute rejection episodes (7 episodes). In that case, antilymphocyte globulin was used twice and anti-CD3 immunoglobulins once. The three patients in that group were treated by chemotherapy and a decrease in immunosuppression.

Regarding the group of NCSM, lung neoplasms were the most common tumors encountered, with a total incidence of 4.1% (11 of 267 patients). Among the remaining 4 tumors, there were 2 urologic tumors, one stomach carcinoma and one epidermoid carcinoma of the pharynx. Among the 11 lung tumors, there were 7 adenocarcinoma, 2 epidermoid carcinoma, one undifferentiated carcinoma and one small cell lung cancer. The clinical profiles of those patients are summarized on Table 2. All the eleven patients were heavy smokers. The interval between transplantation and clinical diagnosis was 35 months (range, 6 to 96 months). A curative resection was possible in 2 (18%) of the eleven patients. Only 3 patients are still alive, 2 of them underwent curative surgery. The 8 patients who died underwent palliative chemotherapy or no treatment (See Table 2). For these 8 patients, the mean interval between diagnosis of malignancy and death was 4.1 months (range 1 to 10 months). Mean survival after lung neoplasm diagnosis was 9.1 months.

3.3. Overall survival

Mean survival after a diagnosis of non cutaneous de novo malignant neoplasm was 11.7 months with a range of 1 to 65 months. The 2-year and 5-year actuarial survivals after transplantation for the study group were 78% and 38%, respectively, compared with 87% and 74% for the population at risk. A comparison of survival between the study group and the population at risk is presented in Fig. 1.

4. Discussion

Compared to graft atherosclerosis which is the most common long term complication of heart transplantation, de novo malignancy is a relatively uncommon complication. Since 1969, when an increased incidence of lymphomas was noted in renal-transplant recipients [10], evidence has accumulated that organ transplantation and the immunosuppressive therapy associated with it, are complicated by an increased incidence of certain cancers. The Cincinnati Transplant Tumor Registry (CTTR) represents the main world database of tumors following organ transplantations [9]. Up to May 1995 the CTTR has data on 8724 cancers that occured de novo after transplantation in 8191 recipients (772 cardiac allograft recipients). These findings indicate that the incidence of cancer is increased 3 to 4-fold in organ allograft recipients compared with age-matched controls in the general population. The major problem of such multi-center registries is that the assessment of the extent of the risk is relied on anecdotal reporting of tumors by many transplant units, often in several countries. The Academic Unit of Surgery from Leeds underlined the fact that the accuracy of such multicentre epidemiological surveys is debatable [5]. Moreover, no breakdown for cardiac recipients is provided from the CTTR.
Table 2
Clinical profiles of heart transplant in whom lung tumors developed

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (months)</th>
<th>Interval from HTX to Dg (months)</th>
<th>Stage of TNM</th>
<th>Tumor Histology</th>
<th>Treatment</th>
<th>Survival after Dg (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>96</td>
<td>T3 N2 M1</td>
<td>Undifferentiated Carcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>5</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>51</td>
<td>T4 N3 M0</td>
<td>Adenocarcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>3</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>41</td>
<td>T1 Ns M1</td>
<td>Epidermoid Carcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>5</td>
<td>Dead</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>22</td>
<td>T1 N0 M0</td>
<td>Adenocarcinoma of the Lung</td>
<td>Surgery</td>
<td>27</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>6</td>
<td>T3 N3 M1</td>
<td>Small Cell lung cancer</td>
<td>Chemotherapy</td>
<td>0</td>
<td>Dead</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>14</td>
<td>T3 N2 M1</td>
<td>Adenocarcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>10</td>
<td>Dead</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>41</td>
<td>T3 N2 M1</td>
<td>Adenocarcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>6</td>
<td>Dead</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>48</td>
<td>T4 N3 M1</td>
<td>Adenocarcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>3</td>
<td>Dead</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>9</td>
<td>T3 N1 M1</td>
<td>Adenocarcinoma of the Lung</td>
<td>Chemotherapy</td>
<td>1</td>
<td>Dead</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>33</td>
<td>T3 N2 M1</td>
<td>Adenocarcinoma of the Lung</td>
<td>Surgery</td>
<td>36</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>27</td>
<td>T2 N0 M0</td>
<td>Epidermoid Carcinoma of the Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recently, Chen et al. and Goldstein et al., reviewed their cardiac transplantation recipients to investigate the incidence and spectrum of noncutaneous malignancies [1,4]. In our study non cutaneous de novo malignancies were identified in 6.7% of patients at risk. The incidence of NCSM (5.6%) is comparable to that of the previously cited author (3.3%) [4] but the incidence of NHL (1.1%) is 4-fold lower in our recipients [1]. Regarding the patient characteristics in our study population, we found two significant difference compared with the population at risk: the mean age is older and the proportion of males is significantly greater than that of the population at risk. Those two points have already been reported [4].

Concerning NHL, we underlined our low incidence as compared to that of other reported series [2,12]. Unfortunately, we have no solid argument to explain that fact. However, we have to considere that the incidence of NHL is strickingly higher in North America than in Europe as it is reported in the multicenter analysis (7634 heart transplant recipients) from Opelz and Henderson [7]: In Europe, during the first transplant year, 1.2% of heart transplant recipients developed NHL. After the first year, the incidence of NHL fell, stabilizing at about 0.3%. The incidence of NHL was about 3-fold higher in North America than in Europe. There is no obvious argument to explain such a difference despite immunosuppressive treatment is generally more aggressive in North America than in Europe. Finally, because of our small series with only 3 cases of NHL, it is difficult to comment on the main questions regarding post transplant lymphoproliferative disorders. We reported only one case of NHL associated with multiple acute rejection episodes and OKT3 therapy. However, there is convincing evidence that the use of the monoclonal preparation OKT3 is associated with an increased prevalence of lymphoproliferative disorders [12]. What about the question whether polyclonal antilymphocyte globulin increases or not the incidence of post transplant lymphoproliferative disorders? The department of cardiothoracic surgery at the Pennsylvania Hospital reported that moderate doses of induction antilymphocyte globulin may facilitate rapid reduction of maintenance cyclosporine and steroid doses. It appears that decreasing the duration of intense immunosuppression reduces the risk of posttransplantation lymphoproliferative disease [2]. Using induction polyclonal antilymphocyte therapy in our immunosuppressive program and regarding our low incidence of NHL, it appears that our results strengthen this hypothesis.

Concerning NCSM, we noticed a high incidence of lung neoplasm (4.1%) as compared to the general population in France. In 1993, crude incidence for primary lung carcinoma was 55.7 per 100 000 among men, and 5.9 for women [8]. Occasional cases of tumors of the lung have been already reported [3,13]. This particular sub-group of lung neoplasms is closely like the one reported by Goldstein [4]. Although the smoking history of all cardiac recipients was not available, all the patients in whom lung neoplasm developed had a heavy smoking history. This suggests that the affected patients had similar risk factors as that of nontransplant lung tumor cohorts. The clinical course of these lung tumor affected patients was accelerated and dreadful. First of all and surprisingly, 2 lung neoplasms developed early after transplantation (respectively 6 and 9 months) in spite of systematic bronchoscopy in the pre-operative screening. This
fact has been already underlined [4]. Second, all the patients excepted 2 of them were affected by a locoregional or advanced extent of disease at presentation. Third, among the 11 lung tumor affected patients, 8 (73%) died within 6 months following the diagnosis. Taken together, these findings suggest that we are in front of patients at risk affected by a « latent lung neoplasm ». Introducing immunosuppression in such patients consist of transforming « latent lung neoplasm » into a patent disease. This hypothesis could be an alternative view of Goldstein et al., who speculated on the potentiation of the carcinogenic effects of cigarette smoking by immunosuppressive therapy [4]. Finally we report a strikingly high proportion of adenocarcinoma of the lung. None published data and none of the multicenter registries reported that fact. This high incidence of adenocarcinoma of the lung should be compared with the increase of such histologic type of lung tumors in the nontransplant general population in the world. However, because of our small series, this result has to be taken carefully.

In conclusion, we have observed a low incidence of Non-Hodgkins’ Lymphoma as compared to the European incidence in such tumors. Using polyclonal antilymphocyte globulin as an immunosuppressive induction therapy may explain a reduction of the following initial immunosuppressive therapy and therefore a reduced incidence of Non-Hodgkins’ Lymphoma. On the contrary, we report a high proportion of lung neoplasms (especially adenocarcinoma). This result could be explained by the high proportion of heavy smokers in our small series. The accelerated and dreadful outcome of these patients have to be considered with the sudden immunosuppressive introduction at the time of transplantation in such patients at risk.

References


Appendix A. Conference discussion

Dr A. Haverich (Hannover, Germany): Did I get it right, 14 out of those 18 patients were smoking?

Dr A. Curtil: Yes, it is true.

Dr A. Haverich: This was pretransplant or post transplant?

Dr A. Curtil: This was pretransplant. They did not continue to smoke after transplantation.

Dr A. Haverich: You are sure?

Dr A. Curtil: It is assumed.

Dr A. Haverich: Okay. Now, your interpretation regarding induction therapy is somewhat new to me. The majority of the studies on post transplant malignant disease actually found a correlation with induction therapy using antilymphocyte globulin preparations is related to a higher incidence of tumor. Could you comment on that?

Dr A. Curtil: As demonstrated by Swinnen et al. [12], it is certainly true that using OKT3 therapy (monoclonal antilymphocyte immunoglobulin) as induction therapy increased the incidence of lymphoproliferative disorder. However, I never saw any publication reporting a higher incidence of non Hodgkin lymphoma associated with the use of moderate doses of polyclonal antilymphocyte immunoglobulin as induction therapy. On the contrary, Dresdale from the Pennsylvania Hospital reported that induction immunotherapy using polyclonal antilymphocyte globulin may reduce the following immunosuppression (cyclosporine and steroid) and therefore may decrease the risk of post transplantation lymphoproliferative disease.

Dr A. Khaghani (Middlesex, UK): I was just going to ask you a question about the second part of your conclusion. You said that the high incidence of adenocarcinoma of the lung was possibly related to smoking. We know that squamous cell carcinoma of the lung is more relevant to smoking, and all the patients we had, normally after transplantation they usually have a squamous cell. I just wonder if you could make a comment on that, of what is the reason behind that idea of smoking is contributing to the development of adenocarcinoma after transplantation?
Dr A. Curtil: Both adenocarcinoma and squamous cell carcinoma of the lung are related to heavy cigarette use. However, I can't tell you any reason to explain the fact that we have a high proportion of adenocarcinoma in our series. I never noticed any reported publication concerning that point. We have to be obviously very careful with such result in our small series.